Abstract—Increased production of organic acid can result in an elevated serum anion gap and may play a role in the development of hypertension. We studied the cross-sectional associations between anion gap and blood pressure and between serum bicarbonate and blood pressure in the 1999-2000 and 2001-2002 National Health and Nutrition Examination Surveys. We included 5043 adult participants who were not taking antihypertensive medications or diuretics and who denied hypertension, cardiovascular disease, diabetes, and other diseases. Linear regression was used to adjust for age, race, body mass index, creatinine, albumin, and other factors. Sample weights were used to produce weighted regression parameters. In the lowest quintile of anion gap, mean values of sodium, chloride, and bicarbonate were 139 mEq/L, 105 mEq/L, and 25 mEq/L, respectively. In the highest quintile, mean values of sodium, chloride, and bicarbonate were 140 mEq/L, 101 mEq/L, and 22 mEq/L, respectively. Mean blood pressure was 118/72 mm Hg. After multivariable adjustment, participants in the highest quintile of anion gap had systolic blood pressure 3.73 mm Hg higher (95% CI: 1.83 to 5.63 mm Hg; P for trend: <0.01) than participants in the lowest quintile. Participants in the highest quintile of bicarbonate had systolic blood pressure 2.73 mm Hg lower (95% CI: 1.26 to 4.20 mm Hg; P for trend: <0.01) than participants in the lowest quintile. No associations were observed between anion gap or bicarbonate and diastolic blood pressure. The results were unchanged after excluding participants with estimated glomerular filtration rate <60 cc/min per 1.73 m². The anion gap is independently associated with higher blood pressure. Further research is needed to elucidate the relation between organic acid and hypertension. (Hypertension. 2007;50:1-5.)

Key Words: epidemiology ■ hypertension ■ anion gap ■ metabolic acidosis ■ NHANES

Hypertension affects >65 million individuals in the United States1,2 and is an important independent risk factor for cardiovascular disease3–6 and renal failure.7–9 The pathogenesis of hypertension is poorly understood and remains under active investigation. It has been suggested that increased production of organic acid may lead to the development of hypertension.10

Metabolic acidosis, increased renal acid excretion, and increased metabolic production of acid have been reported in rat models of hypertension and in salt-sensitive humans. For example, plasma pH and bicarbonate were lower in spontaneously hypertensive rats than in normotensive controls.11,12 Metabolic acidosis preceded the development of hypertension in the hypertensive rats, suggesting that the acid-base changes were not the product of elevated blood pressure or associated renal insufficiency.12 Metabolic studies of rats on both high- and low-salt diets have demonstrated increased urinary acid excretion in salt-sensitive compared with salt-resistant rats.13 Of note, the higher levels of acid excretion in the salt-sensitive rats appeared to be because of increased metabolic production of acid.13 Analogous results have been reported in salt-sensitive humans.14,15

The results of a recent study analyzing the 24-hour excretion of urinary citrate in >3000 men and women are consistent with the hypothesis that higher levels of organic acid production may be related to high blood pressure. The excretion of urinary citrate is regulated most prominently by acid-base status, with acidosis resulting in a marked reduction in citrate excretion.16 After adjustment for age, body mass index (BMI), diet, and other urinary factors, participants with hypocitraturia were 2.5 times more likely to have prevalent hypertension than those without hypocitraturia.17 To date, there have been no population-based studies of acid-base status and blood pressure. An increase in unmeasured anions, as seen in many causes of metabolic acidosis, results in an elevated serum anion gap. We examined the associations between serum anion gap and blood pressure and between serum bicarbonate and blood pressure in the 1999–2000 and 2001–2002 National Health and Nutrition Examination Surveys (NHANES).

Methods

Study Population

We studied participants in NHANES 1999–2000 and 2001–2002. The design and operation of NHANES has been described previously (data downloaded from http://www.cdc.gov/nchs/about/major/
Measurement of Blood Pressure

Blood pressure was determined by mercury sphygmomanometer according to American Heart Association guidelines. Three of four blood pressure determinations (systolic and diastolic) were taken on all of the eligible individuals. The arithmetic mean of blood pressure recordings was used as the blood pressure.

Statistical Analyses

Because older individuals, Mexican Americans, and black individuals were intentionally overrepresented, NHANES 1999–2000 and 2001–2002 were not simple random samples of the US population. Therefore, appropriate sample weights were used to obtain weighted regression estimates, and the final results of our analyses are generalizable to the US population.

For our analyses, we excluded participants with self-reported chronic diseases, including hypertension, chronic kidney disease, diabetes mellitus, congestive heart failure, coronary artery disease, myocardial infarction, angina, cerebrovascular disease, and cancer (except nonmelanoma skin cancer), as well as those taking antihypertensive medications or diuretics. We divided the serum anion gap (except nonmelanoma skin cancer) and individuals with measured albumin <3.5 g/dL and/or measured calcium >10.5 mmol/L, there were 5043 participants remaining in the study population. Characteristics of these participants are shown in Table 1. Because the relations among anion gap, serum bicarbonate, and blood pressure did not vary by sex, results for men and women were combined.

Serum anion gap was positively associated with systolic blood pressure in age-adjusted and multivariable-adjusted analyses (Table 2). After adjusting for age, gender, race, BMI, creatinine, and albumin, systolic blood pressure increased by 0.48 mm Hg (95% CI: 0.28 to 0.69 mm Hg) for each milliequivalent-per-liter increase in serum anion gap. After multivariable adjustment, participants in the highest quintile of anion gap had systolic blood pressure 3.73 mm Hg higher (95% CI: 1.83 to 5.63 mm Hg; P for trend: <0.01) than participants in the lowest quintile. The relation between anion gap and diastolic blood pressure was not statistically significant.

The multivariable-adjusted OR of abnormal blood pressure (systolic blood pressure ≥120; diastolic blood pressure ≥80, or both) was 1.68 (95% CI: 1.18 to 2.41; P for trend: <0.01) for participants in the highest quintile of serum anion gap compared with those in the lowest quintile.

We also evaluated the relation between serum bicarbonate and blood pressure. To determine the association between bicarbonate and blood pressure independent of serum sodium and chloride concentrations, we included serum sodium and chloride in the multivariable models. After adjusting for age, gender, race, BMI, creatinine, albumin, sodium, and chloride, systolic blood pressure increased by 0.46 mm Hg (95% CI: 0.23 to 0.69 mm Hg) for each milliequivalent-per-liter decrease in bicarbonate. After multivariable adjustment, participants in the highest quintile of bicarbonate (mean: 26.8 mEq/L) had systolic blood pressure 2.73 mm Hg lower (95% CI: 1.26 to 4.20 mm Hg; P for trend: <0.01) than participants in the lowest quintile of bicarbonate (mean: 20.2 mEq/L).
relation between bicarbonate and diastolic blood pressure was not statistically significant.

Finally, we performed analyses excluding the 126 participants with chronic kidney disease (defined by calculated GFR <60 cc/min per 1.73 m²) from our sample (Table 3). The results were similar to the primary analysis. After adjusting for age, gender, race, BMI, creatinine, and albumin, participants in the highest quintile of anion gap had systolic blood pressure 3.70 mm Hg higher (95% CI: 1.75 to 5.66 mm Hg; P for trend: <0.01) than participants in the lowest quintile. Further adjustment for smoking, serum calcium, serum potassium, and dietary intake of total protein and potassium did not materially change the results.

Discussion

In adult participants of NHANES 1999–2002, higher levels of serum anion gap were associated with higher blood pressure. This relation was independent of age, gender, race, BMI, and levels of serum creatinine and albumin. Because our study excluded participants who reported cardiovascular disease, hypertension, kidney disease, diabetes, or other diseases and excluded participants taking antihypertensive medications or diuretics, it is unlikely that illness or medication use confounded the observed relation between serum anion gap and blood pressure. Of note, the mean values of serum electrolytes and blood pressure in our study were in ranges considered normal.

The cause of the observed association between higher anion gap and higher blood pressure is unknown. Elevations in the serum anion gap can result from an increase in unmeasured cations or from a decrease in unmeasured anions, as in several causes of metabolic acidosis, or from a decrease in unmeasured cations. In general, reductions in serum calcium and potassium concentrations are unusual causes

### TABLE 1. Cohort Characteristics by Quintile of Anion Gap

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Quintiles of Anion Gap</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1, &lt;10.5 mEq/L</td>
</tr>
<tr>
<td>No.</td>
<td>1001</td>
</tr>
<tr>
<td>Age, y</td>
<td>42.9±0.6</td>
</tr>
<tr>
<td>Female, %</td>
<td>51.1</td>
</tr>
<tr>
<td>Non-Hispanic white, %</td>
<td>73.0</td>
</tr>
<tr>
<td>Non-Hispanic black, %</td>
<td>11.3</td>
</tr>
<tr>
<td>Hispanic, %</td>
<td>13.1</td>
</tr>
<tr>
<td>Other ethnicity/race, %</td>
<td>2.6</td>
</tr>
<tr>
<td>Currently smoking, %</td>
<td>24.4</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.7±0.2</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>4.31±0.03</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>0.87±0.01</td>
</tr>
<tr>
<td>Estimated GFR, cc/min per 1.73 m²</td>
<td>95.1±1.0</td>
</tr>
<tr>
<td>Serum sodium, mEq/L</td>
<td>138.7±0.2</td>
</tr>
<tr>
<td>Serum chloride, mEq/L</td>
<td>104.5±0.2</td>
</tr>
<tr>
<td>Serum bicarbonate, mEq/L</td>
<td>25.2±0.2</td>
</tr>
<tr>
<td>Serum anion gap, mEq/L</td>
<td>9.02±0.11</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>116.6±0.5</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>70.9±0.4</td>
</tr>
</tbody>
</table>

Values are means±SEs except where noted.

### TABLE 2. Predicted Change in Systolic and Diastolic Blood Pressure by Single Units and Quintiles of Anion Gap

<table>
<thead>
<tr>
<th>Anion Gap, mEq/L</th>
<th>Systolic Blood Pressure, mm Hg</th>
<th>Diastolic Blood Pressure, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age-Adjusted</td>
<td>Multivariate*</td>
</tr>
<tr>
<td>Continuous</td>
<td>0.62 (0.43 to 0.81)</td>
<td>0.48 (0.28 to 0.69)</td>
</tr>
<tr>
<td>Quintile 1</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Quintile 2</td>
<td>2.29 (1.21 to 3.37)</td>
<td>1.80 (0.65 to 2.95)</td>
</tr>
<tr>
<td>Quintile 3</td>
<td>2.06 (0.85 to 3.28)</td>
<td>1.72 (0.40 to 3.04)</td>
</tr>
<tr>
<td>Quintile 4</td>
<td>2.68 (1.36 to 3.99)</td>
<td>2.04 (0.95 to 3.13)</td>
</tr>
<tr>
<td>Quintile 5</td>
<td>4.84 (3.05 to 6.63)</td>
<td>3.73 (1.83 to 5.63)</td>
</tr>
</tbody>
</table>

P for trend: <0.01 | <0.01 | 0.07 | 0.34

Values in parentheses are 95% CIs.

*Multivariate models were adjusted for age, gender, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, or other), BMI, serum creatinine, and serum albumin.
of an elevated anion gap, and in our study the relation between anion gap and blood pressure was unchanged after adjustment for these cations. Serum albumin can also affect the anion gap, but we excluded individuals with low serum albumin, and we adjusted for albumin in the multivariate analyses. A mild elevation in anion gap has been reported in metabolic alkalosis, but we are unaware of data linking metabolic alkalosis to higher blood pressure, and in our study higher serum bicarbonate was not associated with higher blood pressure.

It is possible that the participants in our study with higher anion gap had a circulating unmeasured anion that contributed to higher blood pressure. The inverse relation between serum bicarbonate and blood pressure suggests that such an anion, if present, may be the conjugate base of an organic acid. Of interest, metabolic acidosis, increased renal acid excretion, and increased metabolic production of acid have been reported in rat models of hypertension. For example, lower plasma pH and bicarbonate have been reported in spontaneously hypertensive rats and Milan hypertensive rats compared with Wistar Kyoto and Milan normotensive control rats. Metabolic acidosis preceded the development of hypertension in young spontaneously hypertensive rats, suggesting that the acid-base changes were not the product of elevated blood pressure or associated renal insufficiency. Metabolic studies of Dahl/Rapp salt-sensitive and salt-resistant control rats on both high- and low-salt diets have demonstrated increased urinary acid excretion in salt-sensitive compared with salt-resistant control rats. Of note, the higher levels of acid excretion in the Dahl/Rapp salt-sensitive rats appeared to be because of increased metabolic production of acid.

Human data suggesting a possible link between organic acid production and high blood pressure are sparse but provocative. In a metabolic study of 40 healthy normotensive young men consuming controlled diets, there was an inverse association between increases in blood pressure induced by a high-sodium diet and both arterial pH and serum bicarbonate (of note, levels of arterial pH and bicarbonate were in ranges considered normal in both salt-sensitive and salt-resistant participants). The investigators then administered an ammonium chloride load to a subset of these study participants, who again consumed controlled high- and low-sodium diets. There was no difference in renal net acid excretion between the salt-sensitive and salt-resistant groups, suggesting that the relative metabolic acidosis in salt-sensitive individuals was a result of increased production of acid rather than a defect in renal acid excretion. More recent data are also consistent with the hypothesis that increased metabolic production of acid results in higher blood pressure. The excretion of urinary citrate is regulated most prominently by acid-base status (acidosis results in a marked reduction in urinary citrate), and hypertensive individuals excrete less urinary citrate than normotensive control subjects. In >3000 participants in the Nurses’ Health Study I, the Nurses’ Health Study II, and the Health Professionals Follow-up Study, the multivariable ORs of prevalent hypertension for those in the highest quartile of 24-hour urinary citrate excretion compared with the lowest quartile were 0.37 (95% CI: 0.24 to 0.55; P for trend: <0.001) in Nurses’ Health Study I, 0.54 (95% CI: 0.32 to 0.92; P for trend: 0.03) in Nurses’ Health Study II, and 0.27 (95% CI: 0.16 to 0.45; P for trend: <0.001) in Health Professionals Follow-up Study. These results were adjusted for age, weight, the intake of animal protein and potassium, and urinary factors including calcium, citrate, oxalate, uric acid, sodium, magnesium, potassium, phosphorus, creatinine, pH, and total volume. Finally, we suggest, in a broad and purely speculative fashion, that the higher blood pressures observed after administration of sodium chloride versus sodium bicarbonate or sodium citrate may represent a protective effect of alkali on sodium-mediated increases in blood pressure.

Our study has limitations. Because the data are cross-sectional, we cannot conclude that an elevated serum anion gap is a risk factor for the development of higher blood pressure. Instead, it is possible that higher blood pressure results in an elevated anion gap because of an unknown mechanism. An important limitation to any study of serum electrolytes and blood pressure is that reduced kidney function is associated with higher anion gap, lower levels of serum bicarbonate, and elevated blood pressure. Previous NHANES data demonstrated that serum anion gap started to increase and serum bicarbonate levels started to decrease when estimated glomerular filtration was <20 cc/min. However, in our study we excluded participants with self-reported chronic kidney disease, and we adjusted our analyses for serum creatinine. In addition, we performed analyses exclud-
ing participants with chronic kidney disease, as defined by a calculated GFR <60 cc/min per 1.73 m². Another limitation is that medications, such as diuretics, can affect both serum bicarbonate levels and blood pressure. However, we excluded participants who reported the use of such medications. An additional limitation is that study participants were not eating controlled diets. Net endogenous acid production is affected by diet, and dietary factors play an important role in blood pressure. However, the primary dietary determinants of net endogenous acid production are total protein and potassium. However, the primary dietary determinants of net endogenous acid production are total protein and potassium.35 and adjustment for the intake of these factors did not change our results. Finally, we did not have measurements of arterial pH or partial pressure of carbon dioxide, and we did not have urinary parameters to measure renal net acid excretion. Thus, we are unable to fully assess the acid-base status of the participants in the study.

Perspectives
Higher serum anion gap is independently associated with higher blood pressure. Prospective studies of the relation between serum anion gap and incident hypertension are needed. Our data provide support for the hypothesis that increased production of organic acid plays a role in hypertension and should encourage further research into the relation between acid-base metabolism and blood pressure.

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Disclosures
None.

References
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